Remarks

Claims 2 and 15 are pending in the present case. In a non-final Office Action dated August 16, 2007, claims 2 and 15 stand rejected under 35 USC §102(b) as being anticipated by each of TEICHER *et al.* (WO 02/02094 A2) and HEATH *et al.* (US patent no. 5,545,636). Claims 2 and 15 also stand rejected under 35 USC §102(e) as being anticipated by HEATH *et al.* (US patent no. 5,545,636). Finally, claims 2 and 15 stand rejected under 35 USC §103(a) as being obvious over each of TEICHER *et al.* (WO 02/02094 A2) and HEATH *et al.* (US patent no. 5,545,636). Applicants note that an Examiner Interview was conducted via telephone on February 5, 2008. Applicants hereby submit the following arguments and remarks, as discussed in the interview, for consideration in connection with the above-identified patent application.

In view of the reasons set forth below, it is submitted that the rejections are improper and should be withdrawn. Reconsideration and reexamination of the present application is respectfully requested.

35 USC §102(b)—1st Rejection

As used herein, the free base form of 2,5-dione-3-(1-methyl-1H-indol-3-yl)-4-[1-(pyridin-2-ylmethyl)piperidin-4-yl]-1H-indol-3-yl]-1H-pyrrole is referred to as "FB." Claims 2 and 15 of the present invention relate to a particular crystalline form of the mono-hydrochloride salt of FB having a particular X-ray diffraction pattern. That is, the claimed invention relates not merely to a novel salt form of FB (i.e., the mono-hydrochloride salt), but to crystalline forms thereof generally and, specifically, a particular crystalline form thereof.

Claims 2 and 15 stand rejected under 35 USC §102(b) as being anticipated by TEICHER *et al.* (WO 02/02094 A2) A reference can only anticipate a claim if "each and every limitation is found either expressly or inherently in [that] single prior art reference." *Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1360 (Fed. Cir. 1998). Thus, the prior art reference must disclose each and every feature of the claimed invention, either explicitly or inherently. *Glaxo Inc. v. Novopharm* Ltd., 52 F.3d 1043, 1047 (Fed. Cir. 1995).

The Office Action relies on five sections of TEICHER to support the assertion of anticipation:

1. TEICHER lines 1-10, p. 7, "a compound of Formula 1 or a pharmaceutically acceptable salt or solvate thereof," relating generally to salts and solvates of FB through recitation of "a pharmaceutically acceptable salt or solvate thereof."

2. Claims 1, 3-7 and 13 of TEICHER, relating generally to salts and solvates of the FB by recitation of "a pharmaceutically acceptable salt or solvate thereof."

3. TEICHER lines 13-32, p. 8, listing acid addition salts of the FB and showing a preference for hydrochloride salts:

> Because it contains a basic moiety, the compound of Formula 1 can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include such inorganic acids as hydrochloric….Particularly the hydrochloric and mesylate salts are used.

4. TEICHER lines 27-31, p. 11 and TEICHER lines 20-30, p. 14, describing use of a specific dihydrochloride salt of FB:

> The following examples are provided merely to further illustrate the present invention….In each of the following examples, the compound of Formula 1 is administered as the dihydrochloride salt, and the amounts administered are given in terms [sic] amounts of the dihydrochloride salt.
>
> The human SW2 small cell lung carcinoma xenograft was grown subcutaneously in male nude mice and the compound was administered to the animals along with cytotoxic chemotherapy in the sequential treatment regimen. The tumor growth delay produced by administration of 30mg/kg of the compound 317615.2HCl on days 14 through 30 to animals bearing the SW2 tumor was 10 days….

5. TEICHER lines 1-5, p. 9, relating specifically to solvate salts of the FB and their possible source (it should be noted that while the term "solvate" was originally recited in Claim 2, it was excised by subsequent amendment):

> The pharmaceutically acceptable salts of the compound of Formula 1 can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Based on the foregoing evidence, the Office Action concludes:

"In claim 2 the Applicant has cited X-ray diffractions of their crystalline compound. However, since TEICHER *et al* discloses the crystalline forms of this compound and since the compound of prior art exists in crystalline form has the same utility and since no distinction has been made, claim 2 is considered anticipated by the prior art….."

(Office Action p. 4, lines 19, to p. 5, line 3)

These passages from TEICHER generically disclose pharmaceutically acceptable salts or solvates of FB, preferably hydrochloric salts; exemplify one specific, crystalline form of the "dihydrochloride salt" of FB; and suggests, at most, that "solvate salts" of FB could potentially be crystalline. In contrast, Claims 2 and 15 of the present invention relate to a specific crystalline form of a novel mono-hydrochloride salt of FB having a particular X-ray diffraction pattern.

TEICHER has merely disclosed a genus of pharmaceutically acceptable salts or solvates of which hydrochloride salts can be a member (i.e., species). The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992). While admittedly, TEICHER prefers hydrochloric salts of FB, it does not teach mono-hydrochloride salts of FB, more particularly, crystalline mono-hydrochloride salts thereof, and even more particularly, the specific crystalline mono-hydrochloride salt of FB claimed by Applicants or how to make it. In fact, there is no teaching that hydrochloride salts of FB are generally crystalline, rather than amorphous.

Finally, the Office action asserts that "since there is no showing, teaching or comparative data that the prior art hydrochloride is not the same as presently claimed, the claims of the present invention are anticipated by the reference." (Office Action, p. 5, lines 4-6) Applicants are confused by this conclusion since the only form of FB exemplified in TEICHER was the dihydrochloride salt, whereas the claimed invention relates to the mono-hydrochloride salt. The two forms are distinguished by stoichiometry alone. Furthermore, comparative data is generally used to rebut an assertion of *prima facie* obviousness; it is irrelevant to an anticipation analysis. Nevertheless, Applicants' claim a new crystalline form of a previously unknown salt of FB with different properties than the dihydrochloride salt of FB exemplified in TEICHER, as discussed on page 2, lines 8-22 of the specification:

> The dihydrochloric acid salt of the FB is hygroscopic, whereas the monohydrochloride salt of the FB is not significantly hygroscopic. In addition, although the dihydrochloric acid salt of the FB appears to be crystalline by optical light microscopy, more detailed study by X-ray powder diffraction (XRD) has revealed that this material is in fact only poorly crystalline.
>
> Surprisingly, in accordance with the invention, it has now been discovered that the monohydrochloride salt of FB is capable of being reproducibly produced on a commercial scale, is not significantly hygroscopic, is sufficiently stable for use in oral formulations, and can be produced in a highly crystalline state.

In view of the foregoing remarks, Applicants respectfully assert that the rejection is improper and should be withdrawn. Reconsideration is, therefore, kindly solicited.

35 USC §102(b) —2nd Rejection

Claims 2 and 15 of the present invention relate to a particular crystalline form of the mono-hydrochloride salt of FB having a particular X-ray diffraction pattern. That is, the claimed invention relates not merely to a novel salt form of FB (i.e., the mono-hydrochloride salt), but to crystalline forms thereof generally and, more specifically, a particular crystalline form thereof.

Claims 2 and 15 stand rejected under 35 USC §102(b) as being anticipated by TEICHER *et al.* (WO 02/02094 A2) A reference can only anticipate a claim if "each and every limitation is found either expressly or inherently in [that] single prior art reference." *Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1360 (Fed. Cir. 1998). Thus, the prior art reference must disclose each and every feature of the claimed invention, either explicitly or inherently. *Glaxo Inc. v. Novopharm* Ltd., 52 F.3d 1043, 1047 (Fed. Cir. 1995).

The Office Action relies on five sections of HEATH to support the assertion of anticipation:

1. Example 49 in Col. 45 and 46 of HEATH, which discloses "the free base compound of formula FB.

2. Examples 45 and 46 in col. 43 and 44 of HEATH relating to specific derivatives of FB in crystalline form.

3. Formulas II and III in col. 3 and 4 of HEATH relating to a genus of compounds and "pharmaceutically acceptable salts or solvates thereof.

4. A list of acid addition salts of the compounds of Formulas II, III and IV in Col. 3 and 4 including hydrochloric salts.

5. "Examples, abstract and claims" without pointing out with specificity how these sections anticipate Claims 2 and 15.

These passages from HEATH disclose a genus of compounds containing FB or "a salt or solvate thereof" (including hydrochloric salts); exemplify one form of FB; and suggest that certain derivatives of FB can exist in crystalline form. In contrast, Claims 2 and 15 of the present invention relate to a specific crystalline form of a novel mono-hydrochloride salt of the FB having a particular X-ray diffraction pattern.

HEATH has merely disclosed a genus of pharmaceutically acceptable salts of which hydrochloride salts could be a member, i.e., species. The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In*

re Jones, 958 F.2d 347, 350 (Fed. Cir. 1992). Here, the art does not teach mono-hydrochloride salts of FB, more particularly, crystalline mono-hydrochloride salts thereof, and even more particularly, the specific crystalline mono-hydrochloride salt of FB claimed by Applicants or how to make it. In fact, there is no teaching that hydrochloride salts of FB are generally crystalline, rather than amorphous.

The Office Action concludes that "the instant invention is anticipated because applicant provides no evidence that the X-ray diffraction of their compound is different from prior art compound." Applicants are confused by this statement, since the only form of FB exemplified in HEATH was the free base form, whereas the claimed invention relates to the mono-hydrochloride salt. The two forms are distinguished by stoichiometry alone. Furthermore, comparative data is generally used to rebut an assertion of *prima facie* obviousness; it is irrelevant to an anticipation analysis. Nevertheless, Applicants' claim a new crystalline form of a previously unknown salt of FB with different properties than the FB exemplified in HEATH, as discussed on page 2, lines 8-22 of the specification:

> While the FB is undoubtedly a very effective pharmaceutical agent, unexpected difficulties were encountered in its large-scale production. Thus, unpredictable formation of solvates complicated the commercial synthesis to such an extent that it became necessary to develop an alternative form for large-scale commercialization. The monohydrochloride salt of the FB, on the other hand, is capable of being reproducibly produced on a commercial scale and is sufficiently stable for use in oral formulations.
>
> Surprisingly, in accordance with the invention, it has now been discovered that the monohydrochloride salt of FB is capable of being reproducibly produced on a commercial scale, is not significantly hygroscopic, is sufficiently stable for use in oral formulations, and can be produced in a highly crystalline state.

Moreover, the specification provides comparison data distinguishing the claimed mono-hydrochloride crystalline form of FB over a crystalline form of FB (specification p. 8, line 14 to p. 10, line 25)

In view of the foregoing remarks, Applicants respectfully assert that the rejection is improper and should be withdrawn. Reconsideration is, therefore, kindly solicited.

Rejection under 35 USC §102(e)

Claims 2 and 15 stand rejected under 35 USC §102(e) as being anticipated by HEATH *et al.* (US patent no. 5,545,636) on the same grounds as for the 35 USC §102(b) rejection discussed above. As such, the same remarks and arguments asserted by Applicants in that section of this Office Action response apply to the present rejection.

In view of those remarks, Applicants respectfully assert that the rejection is improper and should be withdrawn. Reconsideration is, therefore, kindly solicited.

35 USC §103(a)—1st Rejection

Claims 2 and 15 of the present invention relate to a particular crystalline form of FB having a particular X-ray diffraction pattern. That is, the claimed invention relates not merely to a novel salt form of FB (i.e., the mono-HCl salt), but to a particular crystalline form thereof. Claims 2 and 15 stand rejected under 35 USC §103(a) as being obvious over TEICHER *et al.* (WO 02/02094 A2)

The courts have been consistent in stating that polymorphs are patentable subject matter. The proper test for determining obviousness is whether the prior art would suggest: (a) the existence of another form of the molecule; (b) the structure of that form; and (c) a means of making it; as established in *In re Cofer*:

> "whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form. The new form of the compound set forth in the claims is as much a part of the 'subject matter as a whole' to be compared with the prior art as are other properties of the material which make it useful."

In re Cofer, 148 USPQ 268, 270 (CCPA 1966) (emphasis added). This test was more recently followed in *Ex parte Gala and Dibenedetto*, Appeal No. 2001-0987, US Patent 6,335,347, (Bd. Pat. App. & Int. June 28, 2001) (unpublished). In this way, the courts have been consistent in treating polymorphs as they would any other invention.

Claims 2 and 15 stand rejected under 35 USC §103(a) as being obvious over TEICHER *et al.* based on an assertion that it teaches generally: hydrochloric salts of FB and crystalline forms thereof. Hydrochloric salts of FB are allegedly taught by the following TEICHER passages:

> "The compound of Formula I is used in combination with conventional anti-neoplasm therapies to treat mammals, especially humans, with neoplasia. The procedure for conventional anti-neoplasm therapies, including chemotherapies using anti-neoplastic agents and therapeutic radiation, are readily available, and routinely practiced in the art, e.g., see Harrison's PRINCIPLES OF INTERNAL MEDICINE 11th edition, McGraw-Hill Book /Company. (TEICHER p. 9. lines 6-10)"
>
> A method of treating a neoplasm by administering a combination of an anti-neoplastic agent in combination with FB "or a pharmaceutically acceptable salt or solvate thereof." (Claims 1 and 3-7); A product containing a compound of Formula 1 "or a pharmaceutically acceptable salt or solvate thereof" and an anti-neoplastic agent. (Claim 13)

> Compound of Formula 1 "or a pharmaceutically acceptable salt or solvate thereof." (TEICHER lines 1-10 on p. 7)
>
> "Because it contains a basic moiety, the compound of Formula 1 can also exist as pharmaceutically acceptable acid addition salts. Acids commonly employed to form such salts include such inorganic acids as hydrochloric….Particularly the hydrochloric and mesylate salts are used." (TEICHER lines 13-32 on p. 8)
>
> "The following examples are provided merely to further illustrate the present invention….In each of the following examples, the compound of Formula 1 is administered as the dihydrochloride salt, and the amounts administered are given in terms [sic] amounts of the dihydrochloride salt." (TEICHER lines 27-31 on p. 11)

Applicants agree that these passages taken as a whole teach that hydrochloric salts of FB are preferred, and that the dihydrochloride salt of FB was exemplified.

In support of the assertion that "TEICHER et al teaches the crystalline forms of the compound" (Office Action, p. 9, lines 2-3), the following passage is relied on:

> "The pharmaceutically acceptable salts of the compound of Formula 1 can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, ethyl acetate and the like. Mixtures of such solvates can be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent."

(TEICHER lines 1-5 on p. 9) Applicants note that this passage relates specifically to "solvate salts" of FB, not anhydrous salt forms. In fact, although the term "solvate" was originally recited in Claim 2, it was excised by subsequent amendment because the Examiner objected that the recited X-ray diffraction pattern could not apply to both the anhydrous and solvate forms of the claimed crystalline material. In addition, this passage only provides a possible source of any solvate salts that might form; it makes no assertion as to their probability of formation. Such formation can only be implied. Thus, this passage cannot be read as teaching "the crystalline forms of this compound" generally, as the Office Action concludes. In fact, the only crystalline material taught in TEICHER was one Example of the dihydrochloride salt of FB.

Nevertheless, based on this evidence discussed above, the Office Action concludes that "it would have been obvious at the time of invention to prepare the crystalline pharmaceutically acceptable salts such as hydrochloride salts because …TEICHER *et al* teaches the crystalline forms of this compound." This conclusion of *prima facie* obviousness is clearly erroneous, at least because the Office Action fails to demonstrate (or even address) how the prior art teaches or suggests (1) the specific structure of the claimed material and (2) a procedure for preparing it, as required by *In re Cofer*.

Even assuming, solely for the sake of argument, that the TEICHER teaches hydrochloride salts of FB (generally) and crystalline forms of FB (generally), no rationale is presented as to how one of ordinary skill would predict and prepare the particular crystalline form of the mono-hydrochloride salt of FB claimed by Applicants. In fact, the first procedure for preparing the claimed crystalline material was described in the present specification. (specification p. 14, lines 1-33) The rationale of *In re Heoksema* is applicable here:

> "If the prior art of record fails to disclose or render obvious a method of making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compound overcomes a presumption that the compounds are obvious, based on the close relationships between their structures and those of prior art compounds."

(399 F.2d 269, 274-75, 158 USPQ 597, 601 (CCPA 1968))

In addition to ignoring the test of *In re Cofer*, the Office Action fails to take into account the unpredictability of the crystallization art, such that the structure of any allegedly obvious new form, or its associated properties, cannot be determined by theory. Acid-base reactions (i.e., to form acid addition salts) are predictable in solution based on the relative pKas of the reactants. However, the resulting salts are generally amorphous, and there is no reliable predictor of crystallization. A recent article discussing the possibility of forecasting polymorphs notes that Dr. Sally Price, University College London, and her collaborators had recently launched a multimillion-dollar research effort to develop computer software tools that consider the arrangement of atoms within a compound. (A. Goho, Science News, 166(8):122-124 (2004)) The article goes on to state:

> At the moment, Price says her team can make predictions only for very simple molecules. "Most pharmaceuticals are far more complicated," she says. It could be a decade before such computer predictions can be applied to drug development. In the meantime, the specter of sudden polymorphism will remain a fact of life for pharmaceutical firms.

Id. at 124. The fact that the mere existence of polymorphs cannot be predicted indicates they should be *per se* patentable.

Finally, one of ordinary skill in the art would not have been motivated to seek a new form of FB because, as noted on p. 2, lines 15-18 of the specification, Applicants were the first to discover that the dihydrochloride salt of FB was poorly crystalline and hygroscopic. Under these facts, a general motivation to prepare other selective PKC inhibitor compounds (i.e., derivatives of FB rather than new forms thereof) is insufficient.

Based on the foregoing arguments, claims 2 and 15 cannot be *prima facie* obvious over TEICHER, so that comparative data for rebuttal cannot be required. However, even if the claims were *prima facie* obvious, it would be rebutted by the superior physical properties of the claimed monohydrochloride form of FB over the dihydrochloride form of FB exemplified in TEICHER:

> "It has now been determined that FB-2HCl is hygroscopic. In addition, although FB-2HCl appears to be crystalline by optical light microscopy, more detailed study by X-ray powder diffraction (XRD) has revealed that this material is in fact only poorly crystalline."
>
> "It has now been discovered that the monohydrochloride salt of FB is capable of being reproducibly produced on a commercial scale, is not significantly hygroscopic, is sufficiently stable for use in oral formulations, and can be produced in a highly crystalline state."

(present specification, p. 2, lines 15-22).

In view of the foregoing remarks, Applicants respectfully assert that the rejection is improper and should be withdrawn. Reconsideration is, therefore, kindly solicited.

35 USC §103(a)—2nd Rejection

Claims 2 and 15 of the present invention relate to a particular crystalline form of FB having a particular X-ray diffraction pattern. That is, the claimed invention relates not merely to a novel salt form of FB (i.e., the mono-HCl salt), but to a particular crystalline form thereof. Claims 2 and 15 stand rejected under 35 USC §103(a) as being obvious over HEATH *et al.* (US patent no. 5,545,636)

The courts have been consistent in stating that polymorphs are patentable subject matter. The proper test for determining obviousness is whether the prior art would suggest: (a) the existence of another form of the molecule; (b) the structure of that form; and (c) a means of making it; as established in *In re Cofer*:

> "whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form. The new form of the compound set forth in the claims is as much a part of the 'subject matter as a whole' to be compared with the prior art as are other properties of the material which make it useful."

In re Cofer, 148 USPQ 268, 270 (CCPA 1966) (emphasis added). This test was more recently followed in *Ex parte Gala and Dibenedetto*, Appeal No. 2001-0987, US Patent 6,335,347, (Bd. Pat. App. & Int. June 28, 2001) (unpublished). In this way, the courts have been consistent in treating polymorphs as they would any other invention.

Claims 2 and 15 stand rejected under 35 USC §103(a) as being obvious over HEATH *et al.* based on an assertion that it teaches generally: hydrochloric salts of FB and crystalline forms thereof. Hydrochloric salts of FB are allegedly taught by the following HEATH passages:

> Example 49 in Col. 45 and 46: (FB)
>
> Formulas II and III in col. 3 and 4: (i.e., genus of compounds and "pharmaceutically acceptable salts or solvates thereof."
>
> Abstract (i.e., genus of compounds); Claims (i.e., genus of compounds including FB and a "salt of solvate thereof."); and Examples (i.e., FB and derivatives thereof)
>
> Formulas II, III and IV in Col. 3 and 4, including hydrochloric salts thereof (cited in 102(b) rejection but apparently overlooked here)

Applicants believe that these passages taken as a whole only teach a genus of compounds containing FB or "a salt or solvate thereof" and exemplify one form of FB.

Next, the Office Action asserts that HEATH "teaches crystalline forms of the compound," supported by Examples 45 and 46 in col. 43 and 44 (i.e., crystalline derivatives of FB) specifically, and by the Examples generally. However, all these Examples suggest is that some derivatives of FB can have crystalline forms. The Office Action fails to take into account the unpredictability of the crystallization art, such that the structure of any allegedly obvious new form, or its associated properties, cannot be determined by theory. In comparison, acid-base reactions (i.e., which usually form amorphous acid addition salts) are predictable in solution based on the relative pKas of the reactants.

A recent article discussing the possibility of forecasting polymorphs notes that Dr. Sally Price, University College London, and her collaborators had recently launched a multimillion-dollar research effort to develop computer software tools that consider the arrangement of atoms within a compound. (A. Goho, Science News, 166(8):122-124 (2004)) The article goes on to state:

> At the moment, Price says her team can make predictions only for very simple molecules. "Most pharmaceuticals are far more complicated," she says. It could be a decade before such computer predictions can be applied to drug development. In the meantime, the specter of sudden polymorphism will remain a fact of life for pharmaceutical firms.

Id. at 124. The fact that the mere existence of polymorphs cannot be predicted indicates they should be *per se* patentable.

Based on the evidence discussed, the Office Action concludes that "since the compound is a potent beta-1 and beta-2 isozyme selective PKC inhibitor, one skilled in the art at the time of

invention would have been motivated to prepare the crystalline acid addition salts…such as hydrochloride salts because HEATH teaches the crystalline forms of the compound." This conclusion of *prima facie* obviousness is clearly erroneous at least because the Office Action fails to demonstrate (or even address) how the prior art teaches or suggests (1) the specific structure of the claimed material and (2) a procedure for preparing it, as required by *In re Cofer*.

Even assuming, solely for the sake of argument, that HEATH teaches or suggests hydrochloride salts of FB (generally) and crystalline forms of FB (generally), no rationale is presented as to how one of ordinary skill would predict and prepare the particular crystalline form of the mono-hydrochloride salt of FB claimed by Applicants. In fact, the first procedure for preparing the claimed crystalline material was described in the present specification. (specification p. 14, lines 1-33) The rationale of *In re Heoksema* is applicable here:

> "If the prior art of record fails to disclose or render obvious a method of making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compound overcomes a presumption that the compounds are obvious, based on the close relationships between their structures and those of prior art compounds."

(399 F.2d 269, 274-75, 158 USPQ 597, 601 (CCPA 1968))

Finally, one of ordinary skill in the art would not have been motivated to seek a new form of FB because, as noted on p. 2, lines 8-10 of the specification, Applicants were the first to discover that preparation of the prior art FB form resulted in the unpredictable formation of solvates. Under these facts, a general motivation to prepare other selective PKC inhibitor compounds (i.e., derivatives of FB rather than new forms thereof) is insufficient.

Based on the foregoing arguments, claims 2 and 15 cannot be *prima facie* obvious over HEATH, so that comparative data for rebuttal cannot be required. However, even the claims were *prima facie* obvious, it would be rebutted by the superior physical properties of the claimed material over the material exemplified in HEATH:

> "While FB is undoubtedly a very effective pharmaceutical agent, unexpected difficulties were encountered its large-scale production. Thus, unpredictable formation of solvates complicated the commercial synthesis to such an extent that it became necessary to develop an alternative form for large-scale production." (specification, p. 2, lines 8-11)
>
> "Surprisingly, in accordance with the invention, it has now been discovered that the monohydrochloride salt of FB is capable of being reproducibly produced on a commercial scale, is not significantly hygroscopic, is sufficiently stable for use in oral formulations, and can be produced in a highly crystalline state." (specification, p. 2, lines 19-22)

Moreover, the specification provides comparison data demonstrating the superior physical properties of the claimed mono-hydrochloride form of FB over a crystalline form of FB. (specification, p. 8, line 14 to p. 10, line 25)

In view of the foregoing remarks, Applicants respectfully assert that the rejection is improper and should be withdrawn. Reconsideration is, therefore, kindly solicited.

CONCLUSION

In view of this amendment, Applicants respectfully submit that Claims 2 and 15 set forth an invention that is new, useful, and unobvious, and which is therefore deserving of patent protection. Passage to Issue of the present application is believed to be in order, and is respectfully requested.

Please charge any fees or credit any overpayment in connection with this application which may be required by this or any related paper to Deposit Account No. 05-0840.

If the Examiner has any questions, or would like to discuss any matters in connection with this application, he or she is invited to contact the undersigned at (317) 276-0307.

Respectfully submitted,

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